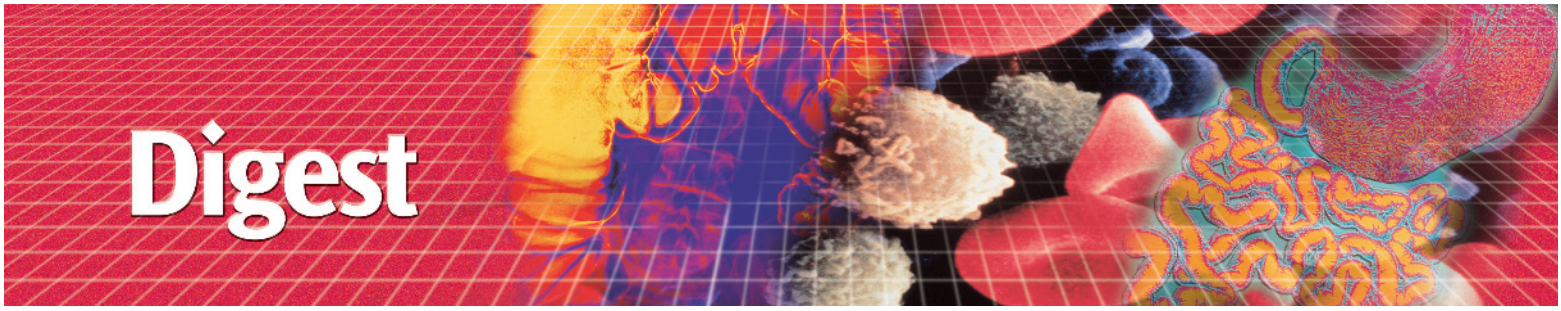
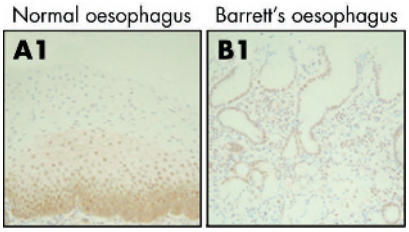


Robin Spiller and Alastair Watson, *Editor and Deputy Editor*

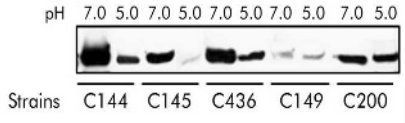


Immunhistochemical analysis for Smad4 in normal squamous and non-dysplastic Barrett's epithelium.

Smad IS INACTIVATED IN BARRETT'S EPITHELIUM

Oesophageal adenocarcinoma arises from columnar epithelium called Barrett's epithelium. The molecular events underlying the metaplasia–dysplasia–adenocarcinoma sequence remain poorly defined, although they are of obvious diagnostic, therapeutic and prognostic importance. One signalling pathway that is often disturbed in gastrointestinal malignancy is the transforming growth factor-β (TGF-β) pathway, but its role in Barrett's epithelium is not understood. TGF-β is a cytokine that binds cell surface receptors, leading to phosphorylation of intracellular signalling molecules called Smad, which translocate to the nucleus and activate a gene programme. Here it is demonstrated that Smad4 is frequently inactivated by methylation, deletion or protein modification. This prevents TGF-β suppressing the proliferation of oesophageal epithelial cells.

See p 764



Effect of low pH on SabA expression by immunoblot analysis. *Helicobacter pylori* was exposed to pH 7.0 and pH 5.0 broth for two hours. Equal amounts of protein were separated on a 10% polyacrylamide gel, transferred to nitrocellulose membranes, and probed with an anti-SabA antiserum (AK278). SabA expression was decreased in acidic conditions in strains C144, C145, and C43.

HELICOBACTER PYLORI OUTER MEMBRANE PROTEIN SABA EXPRESSION IS LINKED TO HIGH INTRAGASTRIC PH

H pylori outer membrane proteins (OMPs), which are though to be important for bacterial adherence, are variably expressed in different strains. Previous studies examining genomic variation have yielded conflicting correlations between OMPs genes and the clinical outcome of infection. This study attempted to overcome these problems by evaluating protein expression of five OMPs (OipA, BabA, BabB and SabA) in 200 patients from Columbia and the USA. OipA, which was closely correlated with CagA, was, as expected, significantly more common in patients with cancer (89%) and duodenal ulcer (88%) compared with those with gastritis (61%). Conversely, SabA was significantly less common in patients with duodenal ulcer (44%) compared with gastritis (66%) and cancer (70%). OipA correlated closely with neutrophil infiltration while SabA was associated with antral intestinal metaplasia and atrophy. SabA expression was rapidly reduced by exposure to low pH, which may account for the clinical correlation, both positive with antral intestinal metaplasia and negative with duodenal ulcer. The authors speculate that the ability to switch in response to pH enhances the ability of the organism to colonise niches in the mucosa with widely variable pH.

See p 775

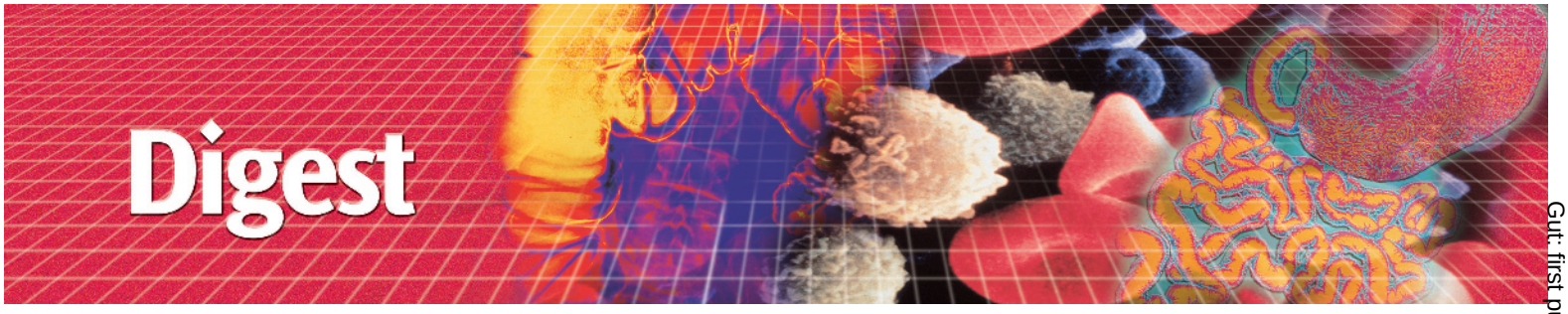
Table 5 Estimates of additive genetic (A), shared environmental (C), and unshared environmental (E) variance components in coeliac disease liability, using two different values for population prevalence

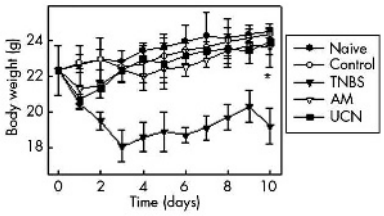
	Variance component		
	A (95% CI)	C (95% CI)	E (95% CI)
Prevalence (threshold)			
1/1000 (3.09)	0.57 (0.32–0.93)	0.42 (0.06–0.67)	0.01 (0.00–0.03)
1/91 (2.29)	0.87 (0.49–1.00)	0.12 (0.00–0.49)	0.01 (0.00–0.05)

INCIDENCE OF COELIAC DISEASE IN TWINS

Coeliac disease is an immune-mediated intolerance to gluten. It is a common condition with two thirds of cases being clinically silent. Both environmental and genetic factors contribute to its aetiology but their relative contribution is not clear. In this study the authors show that its concordance is significantly higher in monozygotic twins than dizygotic twins. In 90% of concordant twins the second twin was diagnosed within 2 years of the first twin's diagnosis. Heritability estimates lie between 57% and 87%, depending on whether the screened population prevalence or the prevalence based on clinical presentation are used for calculation. Similar high rates of heritability are found in other HLA-associated diseases including type I diabetes, Graves' disease and psoriasis.

See p 803





ANTI-INFLAMMATORY UROCORTIN AND ADRENOMEDULIN INCREASE REGULATORY T CELLS

Urocortin 1 (UCN) and adrenomedulin are two recently described neuropeptides related to corticotrophin releasing factor and calcitonin gene related peptide, respectively, which exert anti-inflammatory effects mediated by inhibition of tumour necrosis factor production. This study compared placebo with UCN or adrenomedulin, both given either as a single dose 12 h after the induction of 2,4,6-trinitrobenzene sulfonic acid (TNBS) colitis, or as three daily doses given from days 6–9. As the figure shows, both treatments prevented the weight loss normally associated with acute colitis, with a reduction in mortality from 60% to 20%. There was a clear dose response with a similar benefit when the treatment was given 6 days after TNBS colitis was established. Cytokine production by lamina-propria mononuclear cells fell while interleukin (IL)-10 production rose, associated with a decrease in the number of Th1 cells. Mesenteric lymph node cells showed an increased proportion of CD4+, CD25+, Foxp3+ T cells, which are thought to represent regulatory T cells. The long lasting benefit of a single injection suggests that this might be a potent therapeutic agent.

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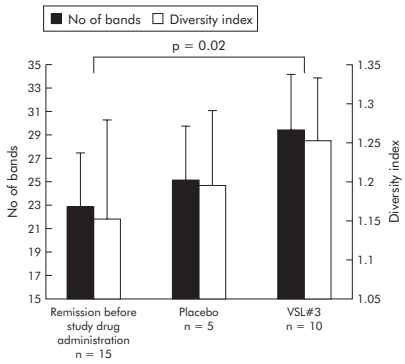
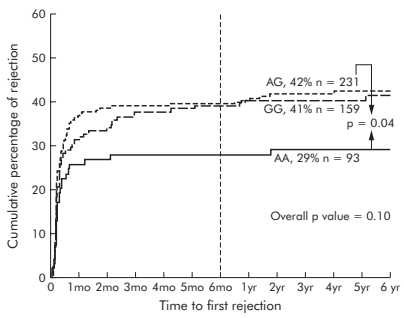


PROBIOTICS INCREASE BACTERIAL DIVERSITY

Probiotics have been shown to be effective in the treatment of pouchitis, but whether this is because of immunosupression or changes in bacterial flora is unknown. This study examined stool and mucosal associated bacteria in patients taking part in a placebo-controlled trial of VSL#3 as maintenance treatment once pouchitis has been controlled by antibiotic treatment. Both bacterial diversity and numbers were low at study entry after antibiotic treatment, an abnormality that was corrected after 2 months of VSL#3 but not placebo. Fluorescent in situ hybridisation (FISH) showed that VSL#3 increased the number of mucosally associated enterobacteriaceae (mainly *E coli*) but not the organisms found in VSL#3. VSL#3 also reduced the diversity index of fundi. It appears, therefore, that VSL#3 treatment corrects the reduction in diversity found in colitis and restores the normal complex enteric flora. This provides a new insight into the complex interactions between members of the commensal flora.

See p 833



Cumulative percentages of acute rejection in liver transplants classified according CTLA-4 +6230G/A.

POLYMORPHISMS OF T CELL REGULATORY GENE CYTOTOXIC T LYMPHOCYTE ANTIGEN 4 (CTLA-4) INFLUENCE THE REJECTION OF LIVER TRANSPLANTS

CTLA-4 is a homologue of CD28. It is expressed on the surface of T cells and is also expressed in a soluble form. It downregulates T cell responses. Polymorphisms of this gene are associated with Graves' disease, type I diabetes, primary biliary cirrhosis and autoimmune hepatitis. This study shows that the +49A/+6230G haplotype reduces production of soluble CTLA-4. This is associated with an increased risk of acute graft rejection even in the presence of immunosuppression.

See p 863